



ELSEVIER

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/vhri

Cost-Utility Analysis of Depot Atypical Antipsychotics for Chronic Schizophrenia in Croatia

Vlado Jukic, MD, PhD¹, Miro Jakovljevic, MD, PhD², Igor Filipic, MD, PhD², Miroslav Herceg, MD, PhD¹, Ante Silic, MD, PhD³, Tatjana Tomljanovic, MD⁴, Roman Zilbershtein, MSc⁵, Rasmus C.D. Jensen, MSc⁶, Michiel E.H. Hemels, MSc, MBA⁶, Thomas R. Einarson, PhD^{7,*}

¹University Psychiatric Hospital "Vrapce," Zagreb, Croatia; ²Department of Psychiatry, University Hospital of Zagreb, Zagreb, Croatia; ³University Psychiatric Hospital "Sv Ivan," Zagreb, Croatia; ⁴Janssen Division of Johnson & Johnson S.E., Zagreb, Croatia; ⁵Pivina Consulting, Inc., Mississauga, Canada; ⁶Janssen Cilag, Birkørød, Denmark; ⁷Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada

ABSTRACT

Objectives: As a nation with a developing economy, Croatia is faced with making choices between pharmaceutical products, including depot injectable antipsychotics. We conducted a pharmacoeconomic analysis to determine the cost-effectiveness of atypical depots in Croatia. **Methods:** A 1-year decision-analytic framework modeled drug use. We determined the average direct cost to the Croatian Institute for Health Insurance of using depot formulations of paliperidone palmitate long-acting injectable (PP-LAI), risperidone LAI (RIS-LAI), or olanzapine LAI (OLZ-LAI). An expert panel plus literature-derived clinical rates populated the core model, along with costs adjusted to 2012 by using the Croatian consumer price index. Clinical outcomes included quality-adjusted life-years, hospitalization rates, emergency room treatment rates, and relapse days. Robustness of results was examined with one-way sensitivity analyses on important inputs; overall, all inputs were varied over 10,000 simulations in a Monte Carlo analysis. **Results:** Costs (quality-adjusted life-years) per patient were €5061 (0.817) for PP-LAI, €5168 (0.807) for RIS-LAI, and

€6410 (0.812) for OLZ-LAI. PP-LAI had the fewest relapse days, emergency room visits, and hospitalizations. Results were sensitive against RIS-LAI with respect to drug costs and adherence rates, but were generally robust overall, dominating OLZ-LAI in 77.3% and RIS-LAI in 56.8% of the simulations. **Conclusions:** PP-LAI dominated the other drugs because it had the lowest cost and best clinical outcomes. Compared with depots of olanzapine and risperidone and oral olanzapine, PP-LAI was the cost-effective atypical LAI for treating chronic schizophrenia in Croatia. Using depot paliperidone in place of either olanzapine or risperidone would reduce the overall costs of caring for these patients.

Keywords: Croatia, long-acting injectable, paliperidone palmitate, pharmacoeconomic analysis, risperidone, schizophrenia.

Copyright © 2013, International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Published by Elsevier Inc.

Introduction

Croatia is a country with a developing economy whose health care system has been developing over some time [1,2]. The Croatian Institute for Health Insurance [3] was established in 1993 to manage the health system that is provided for all citizens. This system is based on a national health insurance model, with compulsory contributions for all employed persons and employers, with co-payments for drugs and services. Noninsured services are paid either out of pocket or through additional voluntary health insurance.

In 1998, a law was passed that guaranteed treatment and also safeguarded the personal rights for persons with schizophrenia requiring involuntary hospitalization [4,5]. Since that time, there has been an increase in both the availability and use of antipsychotics [6,7]. Utilization patterns have changed, with a shift from the older, less expensive first-generation drugs to newer and more costly atypical antipsychotics [6–10].

Problems in drug use, especially nonadherence and polypharmacy, have exacerbated the situation [11,12]. As a result, there have been increasing numbers of hospitalizations [13]. Harvey et al. [14] noted that hospitalization consumed the largest proportion of total health care costs (>30%) in Croatia. In addition, the plan to reintegrate persons with schizophrenia into the community has not been entirely successful [15]. All these factors have served to increase costs for the health system; however, its financial resources are insufficient to cover all the demands. Therefore, cost-effective approaches are needed to maintain and improve the treatment of persons with chronic schizophrenia.

In 2002, the Croatian Institute for Health Insurance funded a project to address rational drug use [14]. A main component was determining how savings could be made by incorporating pharmacoeconomic principles into the selection and purchase of drugs on the Croatian formulary. They observed that "there was

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

* Address correspondence to: Thomas R. Einarson, Leslie Dan Faculty of Pharmacy, 144 College Street, Room 674, University of Toronto, Toronto, ON, Canada M5V 3M8.

E-mail: t.einarson@rogers.com.

2212-1099/\$36.00 – see front matter Copyright © 2013, International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Published by Elsevier Inc.

<http://dx.doi.org/10.1016/j.vhri.2013.06.008>

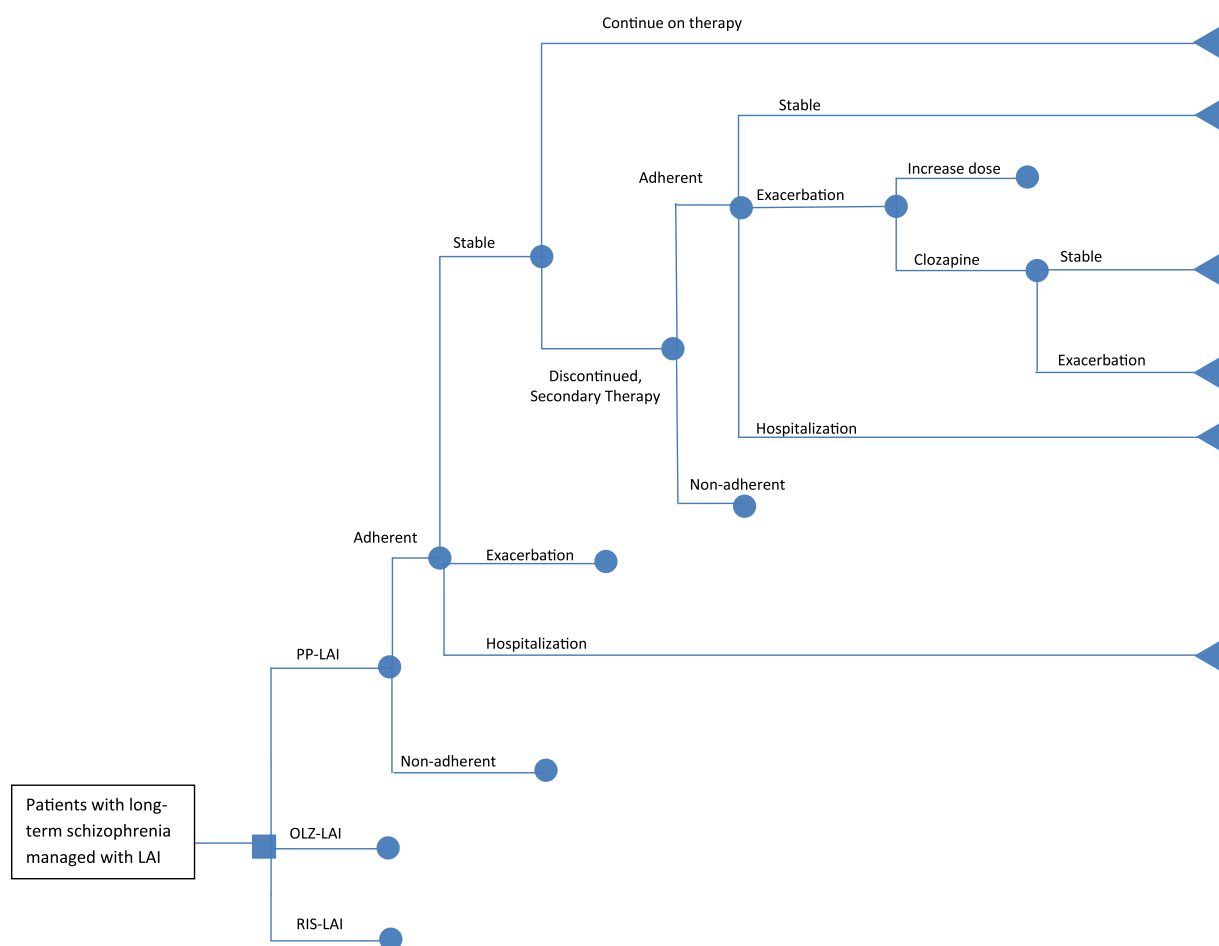


Fig. 1 – Model used for the pharmacoeconomic analysis. LAI, long-acting injectable; OLZ-LAI, olanzapine pamoate long-acting injectable; PP-LAI, paliperidone palmitate long-acting injectable.

a lack of information about what constituted cost-effective treatment appropriate to the Croatian economic situation.” This observation highlights the need for evidence-based information on the cost-effectiveness of psychopharmaceuticals.

At the same time, the rights and dignity of these people must be respected. Two critical aspects are image [16] and quality of life [17,18]. Nawková et al. [19] assessed articles in the lay press in Croatia describing mental health and found that 40 out of the 75 (53%) articles portrayed a negative image. Mentally ill persons were mostly presented as dangerous and involved in aggressive crimes such as homicide (49%) or physical assaults (31%). Martić-Biocina and Barić [12] also identified dissatisfaction with the role of the media in that respect. They also found a high level of stigma toward people with schizophrenia and that it correlated with medication nonadherence and hospitalizations. The same was found with quality-of-life issues [18]. These authors also reported that the atypical antipsychotics were superior to traditional drugs with respect to increasing quality of life in persons with chronic schizophrenia. Jukić et al. [20] suggested that their side-effect profile may be responsible for improved quality of life.

Depot forms of antipsychotic drugs were developed to at least partially address issues of nonadherence [21]. In the past decade, long-acting injectable (LAI) formulations of atypical agents have been marketed to fill a perceived need. Risperidone LAI (RIS-LAI) was the first such drug [22], and has recently been joined by olanzapine LAI (OLZ-LAI) [23] and paliperidone LAI (PP-LAI) [24]. In another country undergoing economic change, a

pharmacoeconomic analysis found that PP-LAI was cost-effective when compared with RIS-LAI [25]. It is not currently known whether the outcomes would be similar in this country. We therefore undertook this research to assess the cost-utility of PP-LAI compared with other LAIs in Croatia from the point of view of the Croatian Institute for Health Insurance.

Methods

Target Population

We examined the use of atypical LAIs in persons with stable chronic schizophrenia but who had a history of relapses and hospitalizations. They have been referred to as “revolving door” patients who are difficult to treat and have problems with adherence to prescribed medications [26,27]. Consequently, they impose a very large burden on health care resources.

Drugs Analyzed

The drug of primary interest was PP-LAI. Comparison drugs included the other atypical depots (i.e., RIS-LAI and OLZ-LAI). According to the product summaries of the European Medicines Agency, PP-LAI (Xeplion) can be dosed monthly [28], OLZ-LAI (Zypadhera) is administered every 2 or 4 weeks [29], and RIS-LAI (Risperdal Consta) requires biweekly injections [30].

Table 1 – Clinical inputs into the model.

LAI antipsychotic	Clinical input (amount/rate)	Rate	Source
Olanzapine	Dose to initialize therapy	300 mg q2 weeks × 3 injections	European Medicines Agency [29]
	Maintenance dose	432 mg q4 weeks	Kane et al. [34]
	Dose for acute relapse	473 mg q4 weeks	Lauriello et al. [35]
	Adherence	0.803	Ascher-Svanum et al. [36]
	Stable disease	0.793	Kane et al. [34]
	ER visits	0.062	Kane et al. [34]
	Hospitalization rate	0.145	Calculation [1 – rates of (ER visits + stable disease)]
Paliperidone	Dose to initialize therapy	150 mg week 1, 100 mg week 2, then 82.8 mg every 4 wk	European Medicines Agency [28], Hough et al. [37]
	Maintenance dose	69.3 mg monthly	Average from Gopal et al. [38] and Fleischhacker et al. [39]
	Dose for acute relapse	84.9 mg monthly	Gopal et al. [40], Pandina et al. [41], Hough et al. [42], Nasrallah et al. [43], Pandina et al. [44]
	Adherence	0.872	RIS-LAI rate from Olivares et al. [45] adjusted via Mehnert and Diels [46]
	Stable disease	0.803	Calculation [1 – rates of (ER visits + hospitalization)]
	ER visits	0.059	Hospital rate × ER:hospital ratio from Ascher-Svanum et al. [36]
	Hospitalization rate	0.138	Hough et al. [37], Gopal et al. [38]
Risperidone	Maintenance dose	40.3 mg biweekly	Fleischhacker et al. [39], Kissling et al. [47], Lee et al. [48], Lindenmayer et al. [49], Olivares et al. [50]
	Dose for acute relapse	50 mg biweekly	Prorated from PP-LAI dose; similar to doses used by Kane et al. [22], Chue et al. [51], Eerdekens et al. [52] who used 58 mg, but 50 mg is the maximum allowable dose [30]
	Adherence	0.823	Olivares et al. [45]
	Stable disease	0.763	Calculation [1 – rates of (ER visits + hospitalization)]
	ER visits	0.071	Hospital rate × ER:hospital ratio from Ascher-Svanum et al. [36]
	Hospitalization rate	0.166	Olivares et al. [50], Weiden and Olsson [53]

ER, emergency room; LAI, long-acting injectable; PP, paliperidone palmitate; RIS, risperidone microspheres.

Model and base case

We adapted a previously validated decision tree [25] for use in Croatia, using input from clinical and administrative experts. Figure 1 depicts the model. To begin the analysis, we start with

an average patient having chronic relapsing schizophrenia but whose disease is currently stabilized. Because of adherence problems, patients are maintained on standard doses of depot antipsychotics. They may be either adherent or nonadherent, as

Table 2 – Cost inputs (2012€).

Resource	Item	Unit	Cost (€)	Source
Drugs	Olanzapine depot	mg	3.50	Croatian Official Gazette [58]
	Risperidone depot	mg	3.50	Croatian Official Gazette [58]
	Paliperidone depot	mg	3.76	Croatian Official Gazette [58]
	Olanzapine tablets	mg	0.21	Croatian Official Gazette [58]
	Risperidone tablets	mg	0.20	Croatian Official Gazette [58]
	Clozapine tablets	mg	0.0036	Croatian Official Gazette [58]
Medical	Primary care physician	1 visit	16.62	Local medical price list
	Psychiatrist outpatient visit	1 visit	14.10	Vrapče hospital price list
	Psychiatric nurse	1 h	7.45	Vrapče hospital price list
Hospital	Emergency room	1 visit	230.32	Vrapče hospital price list
	Hospital bed acute care	1 d	96.81	Vrapče hospital price list
	Hospital long-term bed	1 d	33.51	Vrapče hospital price list
	Day care visit	1 d	26.20	Vrapče hospital price list

Table 3 – Clinical and economic outputs from the decision tree model analysis for Croatia.

Drug	Total cost per patient (€)*	Days in remission	Emergency room visits	Hospitalizations	Total QALYs per patient	Incremental cost per patient (€)†	Incremental QALYs per patient†	Economic conclusion
PP-LAI	5061	329.3	0.129	0.252	0.817			Dominant‡
RIS-LAI	5168	322.8	0.148	0.305	0.807	–107	0.010	Dominated
OLZ-LAI	6410	325.5	0.143	0.280	0.812	–1349	0.005	Dominated

LAI, long-acting injectable; PP, paliperidone palmitate; RIS, risperidone microspheres; QALYs, quality-adjusted life-years.

* All costs are in 2012 euros.

† Because of dominance, comparisons are against PP-LAI.

‡ Has lowest cost and highest QALYs and therefore is the drug of choice.

per published rates and expert opinion. Some will continue in the stable state, while the rest will relapse. All relapsers would be seen at the emergency room, and the more severe cases would be admitted to the acute psychiatric unit. Those unable or unwilling to tolerate the initial treatment would be switched. Those discontinuing PP-LAI or RIS-LAI would then receive OLZ-LAI, and those switching from OLZ-LAI would receive PP-LAI; discontinuers of oral OLZ would receive RIS-LAI. Patients who failed two different drugs would be given clozapine, in accordance with National Institute for Health and Clinical Excellence guidelines [31] and local practice using doses reported in the literature [32,33].

Clinical Inputs

Table 1 lists the clinical inputs used in this model, by drug, as well as the sources of information [22,28–30,34–53]. The doses of drugs used were derived from randomized clinical trials and long-term studies published in the literature. Where data were presented for nonadherent patients, we extracted rates from the published articles. In other cases, we used either the rates for placebo in trials (e.g., PP-LAI; OLZ-LAI assumed equal) or we calculated rates by using the ratio of adherent: nonadherent patients from Weiden and Olfson [53] (e.g., RIS-LAI).

With each drug, adjunct therapy was added, in accordance with typical clinical trials. Gopal et al. [38] indicated that PP-LAI was augmented with oral risperidone in a dose of 6.8 mg/d for 30.5 days. In a similar trial, Möller et al. [54] reported that 22% of the patients receiving RIS-LAI required oral supplementation with 3.2 mg/d for 43 days. Ascher-Svanum et al. [55] noted that OLZ-LAI required 10.8 mg/d for 31 days in 21% of the patients.

Some economic analyses have used standard doses such as defined daily doses (DDD) [56]; however, DDDs reflect the average dose when used for the most common indication. It should be remembered that we are dealing with revolving door patients who comprise only a subset of patients who represent the extreme of the spectrum. Thus, we feel that DDDs would underestimate the doses used in actual practice when managing such problematic patients.

In calculating adherence rates, we used experience from large observational studies. The rate for RIS-LAI was taken from a large patient registry ($n = 1648$) of patients with longstanding schizophrenia [45]. Because there was insufficient long-term experience with PP-LAI, that rate was adjusted by using results from the study by Mehnert and Diels [46]. They compared adherence between RIS-LAI when administered monthly and twice weekly, finding a minimum of 5.1% increase in adherence with monthly injections. That factor was applied to PP-LAI, which is administered monthly and is a metabolite of RIS-LAI, thereby having the same adverse-event profile. For OLZ-LAI, we used the rate from a large cohort ($n = 1906$). Even though that rate was with oral drugs (which normally have lower adherence rates than do depots), we used that value of 80.2% because it was higher than the 72.7% rate in 931 patients found with the depot form by Ascher-Svanum et al. [57], and was quite similar to the rates of other depot atypicals.

Cost Inputs

We considered all direct costs from the viewpoint of the National Health Service of Croatia, as presented in Table 2 [58] (local medical price list and Vrapče hospital price list). We did not include indirect costs such as time lost from work, because very few of these people participate fully in the workforce. A multicountry study in Europe reported that less than 10% of

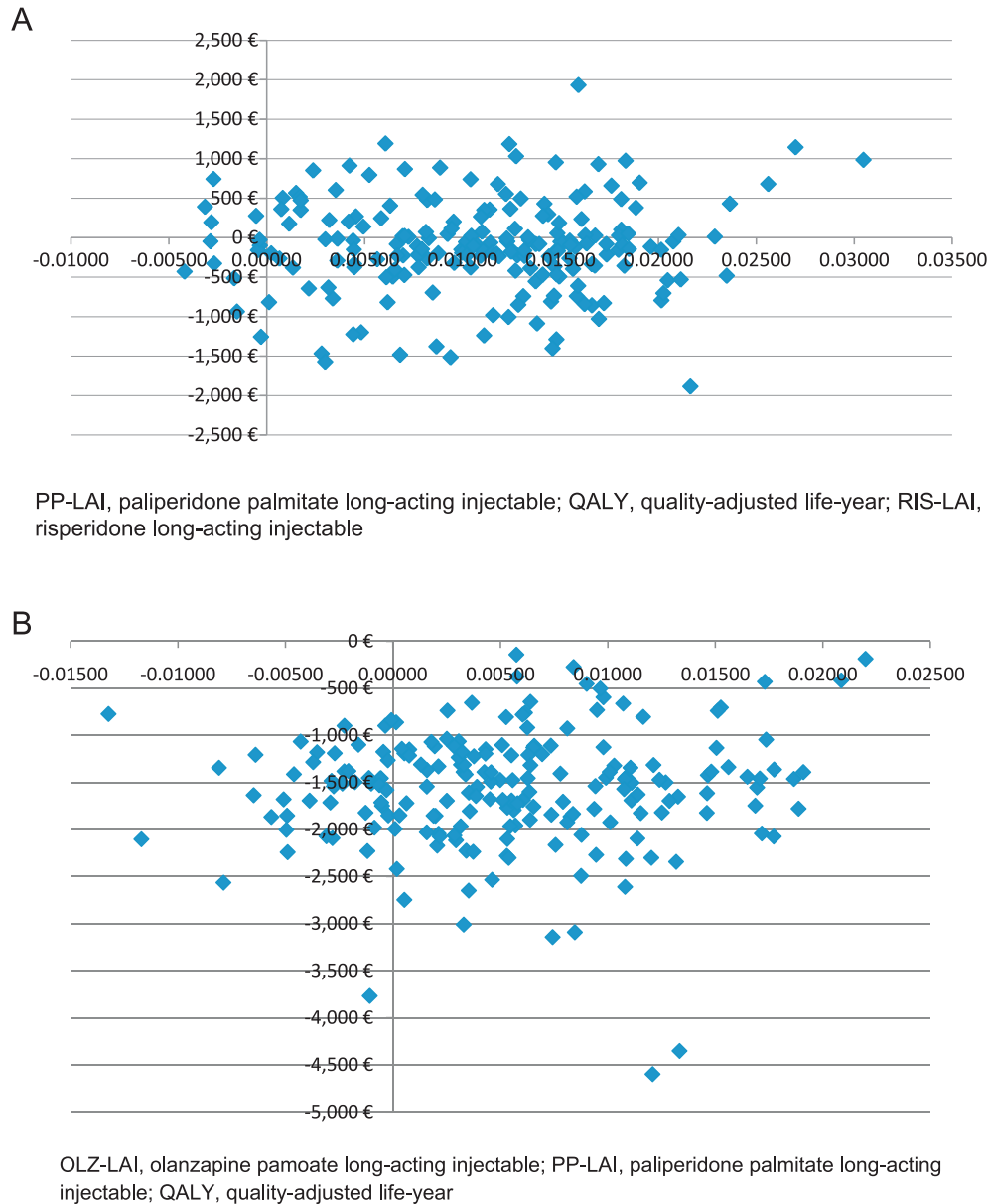


Fig. 2 – Cloud diagram from the probabilistic sensitivity analysis comparing incremental costs (Y axis) and QALYs (X axis) between (A) PP-LAI and RIS-LAI and (B) PP-LAI and OLZ-LAI. OLZ-LAI, olanzapine pamoate long-acting injectable; PP-LAI, paliperidone palmitate long-acting injectable; QALY, quality-adjusted life-year; RIS-LAI, risperidone long-acting injectable.

3996 persons with schizophrenia were employed full-time and another 12.3% worked part-time [59]. We did not apply discounting because the analytic time horizon was 1 year. Prices were taken from current lists or from the literature, and then inflated to 2011 euros by using the consumer price index for Croatia [60].

Utilities

Utilities for the analysis were obtained from the literature; values obtained were simply averaged [61–65]. Stable disease had a utility of 0.890; an exacerbation requiring outpatient treatment at the hospital emergency room had a utility of 0.659 for emergency room exacerbation and 0.490 for hospitalization.

Analysis and Outputs

No official guidelines currently exist for pharmacoeconomic analyses in Croatia. We therefore used a standard approach that had been used in previous analyses in Europe [25]. The decision tree produced expected outcomes for the average patient treated with average doses of each drug. These outcomes included the cost per patient treated, measured in 2012 euros, as well as numbers of hospitalizations, emergency room visits, days with stable disease, and quality-adjusted life-years (QALYs) for each drug. The economic outcome of prime interest was the incremental cost per QALY.

We explored the effect of variations in input values on outputs by applying one-way sensitivity analyses on all important inputs such as costs and clinical rates. Break-even analysis identified the points where outcomes changed qualitatively. We

also conducted a set of pairwise probabilistic analyses by using 10,000 Monte Carlo simulations on all inputs and standard distributions (i.e., beta for rates and gamma for costs) [66]. Proportions of incremental cost-effectiveness ratios falling into each of the four major quadrants (cost vs. QALYs) were calculated and compared.

Results

Results of the base-case analysis appear in Table 3. PP-LAI had the lowest overall cost to treat one patient for 1 year (€5061), followed by RIS-LAI (€5168), with OLZ-LAI costing the most (€6410). Clinical outcomes were also better in all cases for PP-LAI; it had the most days in remission and the fewest hospitalizations and emergency room visits. Also, it was associated with the highest QALY score, but differences for this outcome were not large. Because its cost was lowest and QALYs (and other beneficial clinical outcomes) highest, it dominated the other drugs. That is, it should be considered the preferred choice.

In one-way sensitivity analyses, PP-LAI was not sensitive to changes in cost relative to OLZ-LAI. Its cost would need to increase 64% or that of OLZ-LAI decrease by 54% to lose its dominance. However, it would not dominate RIS-LAI with a 4% increase in the cost of PP-LAI or a 4.4% decrease in the cost of RIS-LAI. If the unit cost of PP-LAI were equal to that of RIS-LAI, the expected cost/patient would decline to €4756. Results were sensitive to reasonable changes in adherence rate ($\pm 10\%$ for OLZ-LAI and $\pm 18\%$ for RIS-LAI). Hospitalization rates were not sensitive.

Figure 2A,B depicts results from the probabilistic sensitivity analyses. PP-LAI dominated OLZ-LAI in about 77.3% of the simulations and RIS-LAI in 56.8% of the simulations. It was cost-effective (i.e., incremental cost-effectiveness ratios $< €30,000$) compared with RIS-LAI in another 37% of the trials (overall 93%). However, PP-LAI was dominated in 1.3% of the 20,000 iterations, in total.

Discussion

A search of the literature could find no examples of pharmacoeconomic analyses that examined the pharmacotherapy of schizophrenia in Croatia. Therefore, we believe that this is the first such analysis. Because decision makers and health care providers are being faced with increasing demands from patients and their advocates without a corresponding increase in revenues, they must take advantage of these quantitative approaches to aid in selecting what to fund. Relying solely on acquisition prices of drugs, services, or other products can be misleading because all factors impacting the choice are not being considered. Because of enhanced efficacy, a drug with a higher price may be the best choice if it prevents the consumption of other resources, such as hospitalization.

In this analysis, PP-LAI dominated the other available atypical LAIs. Results could change against RIS-LAI with changes in cost or against OLZ-LAI with changes in adherence. The overall probabilistic sensitivity analyses, however, did indicate that PP-LAI would be the drug of choice in the majority of cases.

In addition to the clinical and economic advantages, there is an advantage for PP-LAI with respect to convenience. This drug may be administered monthly, while its nearest competitor, RIS-LAI, must be given every 2 weeks. Monthly dosing would seem to be the preferable situation for both the patient and the busy practitioner.

This analysis has some limitations, which should be noted. Rates of adherence and hospitalization were taken from the literature and were assumed to apply as well in this country. We considered only persons with chronic schizophrenia in a stable state. Those who are hospitalized or experiencing an acute exacerbation of symptoms would require more aggressive treatment; therefore, costs and outcomes might vary.

We did not consider the treatment of adverse events other than postinjection syndrome in this analysis for a number of reasons. First, these events are quite common in all antipsychotic drugs. Many of these problems can be managed by reducing the dose or changing to another drug. Also, these patients are required to visit their physician or other practitioner (e.g., psychiatric nurse or psychologist) on a regular basis, and so they would not likely incur extra visits because of adverse events. In addition, many require treatment with drugs (e.g., anticholinergics) that are very inexpensive and add little to the overall cost of care, especially on a comparative basis. Finally, reports from official agencies have concluded that adverse events associated with these drugs have little appreciable impact overall [67,68].

Conclusions

In this analysis, we found that PP-LAI was the dominant choice for treating chronic relapsing schizophrenia in Croatia. Its higher acquisition cost was more than offset by reductions in other health care areas, such as decreased hospitalizations, visits to emergency room, and visits to other health care practitioners. Results were sensitive to minor changes in adherence rates.

Source of financial support: This study was funded by Janssen A/S, Beerse, Belgium. Dr. Tomljanovic, Mr. Rasmussen, and Mr. Hemels are all employees of Janssen. Dr. Einarson received funding for this research. Mr. Zilbershtein is an employee of Pivina Consulting, Inc., who received funding for this research.

REFERENCES

- [1] European Observatory on Health Care Systems. Health Care Systems in Transition: Croatia (2nd ed.). Copenhagen: WHO Regional Office for Europe, 1999. Available from: http://www.euro.who.int/_data/assets/pdf_file/0018/75150/E68394.pdf. [Accessed March 16, 2012].
- [2] Mastilica M, Kušec S. Croatian healthcare system in transition, from the perspective of users. *BMJ* 2005;331:223–7.
- [3] Croatian Institute of Health Insurance. Available from: <http://www.hzzo-net.hr>. [Accessed May 3, 2012].
- [4] Jukić V, Goreta M, Kozumplik O, et al. Implementation of first Croatian Law on Protection of Persons with Mental Disorders. *Coll Antropol* 2005;29:543–9.
- [5] Kozumplik O, Jukić V, Goreta M. Involuntary hospitalizations of patients with mental disorders in Vrapce Psychiatric Hospital: five years of implementation of the first Croatian law on protection of persons with mental disorders. *Croat Med J* 2003;44:601–5.
- [6] Jukić V, Herceg M, Savić A. Availability of psychiatric medications to Croatian healthcare users and the influence of availability of atypical antipsychotics on psychiatric hospital morbidity. *Psychiatr Danub* 2011;23:320–4.
- [7] Jukić V, Savić A, Herceg M. Availability of new psychiatric medications, especially antipsychotics, in context of patient rights and destigmatization of psychiatric patients. *Psychiatr Danub* 2011;23:316–9.
- [8] Jukić V, Herceg M, Brecić P, et al. Dynamic in prescribing antipsychotic drugs during five year period (2001–2005) in the Psychiatric Hospital Vrapce, Zagreb, Croatia. *Coll Antropol* 2008;32(Suppl 1):211–3.
- [9] Štimac D, Čulig J. Outpatient utilization of psychopharmaceuticals in the city of Zagreb 2001–2006. *Psychiatr Danub* 2009;21:56–64.
- [10] Štimac D, Vukusić I, Čulig J, et al. Outpatient utilization of psychopharmaceuticals: comparison between Croatia and Scandinavian countries (2001–2003). *Coll Antropol* 2009;33:237–43.
- [11] Loga-Zec S, Loga S. Polypharmacy in the treatment of schizophrenic patients in three university centers in the Federation of Bosnia and Herzegovina (F/BH). *Psychiatr Danub* 2011;23:60–3.

- [12] Martić-Biocina S, Barić V. Factors important for compliance among Croatian patients suffering from schizophrenia—how to improve psychiatric services in Croatia? *Psychiatr Danub* 2005;17:36–41.
- [13] Bilić P, Ivanis A, Vidović D, Jukić V. Changing the structure of the hospitalized patients at the Psychiatric Clinic Vrapce. *Srp Arh Celok Lek* 2011;139(Suppl 1):33–5.
- [14] Harvey K, Kalanj K, Stevanović R. Croatian pharmaceutical sector reform project: rational drug use. *Croat Med J* 2004;45:611–9.
- [15] Jukić V. (Re)Integration of mental patients—mixed media messages. *Psychiatr Danub* 2008;20:433–6.
- [16] Bilić B, Georgaca E. Representations of “mental illness” in Serbian newspapers: a critical discourse analysis. *Qual Res Psychol* 2007;4:167–86.
- [17] Pesek MB. Therapy and quality of life of patients with psychosis. *Psychiatr Danub* 2009;21(Suppl. 1):146–8.
- [18] Jašović-Gašić M, Lačković M, Dunjić-Kostić B, et al. Critical review of studies on quality of life in psychiatric patients published in Serbian medical journals from 2000 to 2009. *Psychiatr Danub* 2010;22:488–94.
- [19] Nawková L, Nawka A, Adámková T, et al. The picture of mental health/illness in the printed media in three central European countries. *J Health Commun* 2012;17:22–40.
- [20] Jukić V, Barić V, Culav-Sumić J, et al. The impact of novel antipsychotic drugs on quality of life among people suffering from schizophrenia. *Coll Antropol* 2003;27(Suppl. 1):119–24.
- [21] Nasrallah H. The case for long-acting antipsychotic agents in the post-CATIE era. *Acta Psychiatr Scand* 2007;115:60–267.
- [22] Kane J, Eerdekens M, Lindenmayer J-P, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. *Am J Psychiatry* 2003;60:1125–32.
- [23] European Medicines Agency. Assessment report for Zypadhera. Doc. Ref EMEA/608654/2008. Procedure No. EMEA/H/C/000890. 2008:1–63. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000890/WC500054428.pdf. [Accessed March 3, 2012].
- [24] European Medicines Agency. Xeplion® opinion 17-12-2010. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002105/smops/Positive/human_smop_000162.jsp&murl=menus/medicines/medicines. [Accessed March 3, 2012].
- [25] Einarson TR, Geitona M, Chaidemenos A, et al. Pharmacoeconomic analysis of paliperidone palmitate for treating schizophrenia in Greece. *Ann Gen Psychiatry* 2012;11:18.
- [26] Haywood TW, Kravitz HM, Grossman LS, et al. Predicting the “revolving door” phenomenon among patients with schizophrenic, schizoaffective, and affective disorders. *Am J Psychiatry* 1995;152:856–61.
- [27] Weiden P, Glazer W. Assessment and treatment selection for “revolving door” inpatients with schizophrenia. *Psychiatr Q* 1997;68:377–92.
- [28] European Medicines Agency. Xeplion® summary of product characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002105/WC500103317.pdf. [Accessed March 3, 2012].
- [29] European Medicines Agency. Zypadhera® summary of product characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000890/WC500054429.pdf. [Accessed March 3, 2012].
- [30] European Medicines Agency. Risperdal Consta® summary of product characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Risperdal_Consta_30/WC500008170.pdf. [Accessed March 3, 2012].
- [31] National Institute for Health and Care Excellence. Schizophrenia: core interventions in the treatment and management of schizophrenia in adults in primary and secondary care. NICE Clinical Guideline 82 (update). Available from: www.nice.org.uk. [Accessed April 4, 2012].
- [32] Simonsen E, Friis S, Opjordsmoen S, et al. Early identification of non-remission in first-episode psychosis in a two-year outcome study. *Acta Psychiatr Scand* 2010;122:375–83.
- [33] Wahlbeck K, Cheine M, Essali A, Adams C. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. *Am J Psychiatry* 1999;156:990–9.
- [34] Kane J, Detke H, Naber D, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry* 2010;167:181–9.
- [35] Lauriello J, Lambert T, Andersen S, et al. An 8-week, double-blind, randomized, placebo controlled study of olanzapine long-acting injection in acutely ill patients with schizophrenia. *J Clin Psychiatry* 2008;69:790–9.
- [36] Ascher-Svanum H, Faries D, Zhu B, et al. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. *J Clin Psychiatry* 2006;67:453–60.
- [37] Hough D, Gopal S, Vijapurkar U, et al. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. *Schiz Res* 2010;116:107–17.
- [38] Gopal S, Vijapurkar U, Lim P, et al. A 52-week open-label study of the safety and tolerability of paliperidone palmitate in patients with schizophrenia. *J Psychopharmacol* 2010;25:685–97.
- [39] Fleischhacker W, Gopal S, Lane R, et al. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. *Int J Neuropsychopharmacol* 2011; [Epub ahead of print].
- [40] Gopal S, Hough D, Xu H, et al. Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. *Int Clin Psychopharmacol* 2010;25:247–56.
- [41] Pandina GJ, Lane R, Gopal S, et al. A double-blind study of paliperidone palmitate and risperidone long-acting injectable in adults with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;35:218–26.
- [42] Hough D, Lindenmayer J-P, Gopal S, et al. Safety and tolerability of deltoid and gluteal injections of paliperidone palmitate in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2009;33:1022–31.
- [43] Nasrallah H, Gopal S, Gassmann-Mayer C, et al. A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. *Neuropsychopharmacology* 2010;35:2072–82.
- [44] Pandina GJ, Lindenmayer J-P, Lull JM, et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. *J Clin Psychiatry* 2010;30:235–44.
- [45] Olivares J, Peuskens J, Pecanek J, et al. Clinical and resource-use outcomes of risperidone long-acting injection in recent and long-term diagnosed schizophrenia patients: results from a multinational electronic registry. *Curr Med Res Opin* 2009;25:2197–206.
- [46] Mehnert A, Diels J. Impact of administration interval on treatment retention with long-acting antipsychotics in schizophrenia. Presented at the Tenth Workshop on Costs and Assessment in Psychiatry-Mental Health Policy and Economics, March 25–27, 2011, Venice, Italy.
- [47] Kissling W, Heres S, Lloyd K, et al. Direct transition to long-acting risperidone—analysis of long-term efficacy. *J Psychopharmacol* 2005;19:15–21.
- [48] Lee M, Ko Y, Lee S, et al. Long-term treatment with long-acting risperidone in Korean patients with schizophrenia. *Hum Psychopharmacol* 2006;21:399–407.
- [49] Lindenmayer J-P, Khan A, Eerdekens M, et al. Long-term safety and tolerability of long-acting injectable risperidone in patients with schizophrenia or schizoaffective disorder. *Eur Neuropsychopharmacol* 2007;17:138–44.
- [50] Olivares JM, Rodrigues-Morales A, Diels J, et al. Long-term outcomes in patients with schizophrenia treated with risperidone long-acting injection or oral antipsychotics in Spain: results from the electronic Schizophrenia Treatment Adherence Registry (e-STAR). *Eur Psychiatry* 2009;24:287–96.
- [51] Chue P, Eerdekens M, Augustyns I, et al. Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets. *Eur Neuropsychopharmacol* 2005;15:111–7.
- [52] Eerdekens M, Van Hove I, Remmerie B, Mannaert E. Pharmacokinetics and tolerability of long-acting risperidone in schizophrenia. *Schizophr Res* 2004;70:91–100.
- [53] Weiden PJ, Olsson M. Cost of relapse in schizophrenia. *Schiz Bull* 1995;21:419–29.
- [54] Möller HJ, Llorca PM, Sacchetti E, et al. Efficacy and safety of direct transition to risperidone long-acting injectable in patients treated with various antipsychotic therapies. *Int Clin Psychopharmacol* 2005;20:121–30.
- [55] Ascher-Svanum H, Peng X, Montgomery W, et al. Assessing the infrequent oral supplementation of olanzapine long-acting injection in the treatment of schizophrenia. *Eur Psychiatry* 2011;26:313–9.
- [56] ATC/DDD Index 2011. Available from: http://www.whocc.no/atc_ddd_index/. [Accessed May 3, 2012].
- [57] Ascher-Svanum H, Montgomery WS, McDonnell DP, et al. Treatment-completion rates with olanzapine long-acting injection versus risperidone long-acting injection in a 12-month, open-label treatment of schizophrenia: indirect, exploratory comparisons. *Int J Gen Med* 2012;5:391–8.
- [58] Croatian Institute of Health Insurance: List of Drugs. Official Gazette No. 69, 2010; No. 54, 2011 and No. 48 2012.
- [59] Papageorgiou G, Cañas F, Zink M, Rossi A. Country differences in patient characteristics and treatment in schizophrenia: data from a physician-based survey in Europe. *Eur Psychiatry* 2011;26(Suppl. 1):17–28.
- [60] Consumer price index for Croatia. Available from: <http://www.indexmundi.com/facts/croatia/consumer-price-index>. [Accessed May 3, 2012].

- [61] Briggs A, Wild D, Lees M, et al. Impact of schizophrenia and schizophrenia treatment-related adverse events on quality of life: direct utility elicitation. *Health Qual Life Outcomes* 2008;6:105.
- [62] Cummins C, Stevens A, Kisely S. The Use of Olanzapine as a First and Second Choice Treatment in Schizophrenia. Birmingham, UK: Department of Public Health & Epidemiology, University of Birmingham, 1998. A West Midlands Development and Evaluation Committee Report.
- [63] Lenert L, Sturley A, Rapaport M, et al. Public preferences for health states with schizophrenia and a mapping function to estimate utilities from positive and negative symptom scale scores. *Schiz Res* 2004;71:155–65.
- [64] Oh P, Lanctôt K, Mittmann N, et al. Cost-utility of risperidone compared with standard conventional antipsychotics in chronic schizophrenia. *J Med Econ* 2001;4:137–56.
- [65] Revicki D, Shakespeare A, Kind P. Preferences for schizophrenia-related health states: a comparison of patients, caregivers and psychiatrists. *Int Clin Psychopharmacol* 1996;11:101–8.
- [66] Johnson ML, Crown W, Martin BC, et al. Good research practices for comparative effectiveness research: analytic methods to improve causal inference from nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force report—part III. *Value Health* 2009;12:1062–73.
- [67] All Wales Medicines Strategy Group. Final appraisal report: olanzapine depot (ZypAdhera®), Lilly UK. Advice No: 1510 – October 2010. Available from: [http://www.wales.nhs.uk/sites3/Documents/371/olanzapine%20depot%20\(ZypAdhera\)%20schizophrenia.pdf](http://www.wales.nhs.uk/sites3/Documents/371/olanzapine%20depot%20(ZypAdhera)%20schizophrenia.pdf). [Accessed July 7, 2012].
- [68] Farahati F, Boucher M, Moulton K, et al. Atypical Antipsychotic Monotherapy for Schizophrenia: Clinical Review and Economic Evaluation of First Year of Treatment (Technology report number 91). Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health, 2007.